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Histologic characteristics of skin cancer in Hiroshima and Nagasaki: Background incidence and radiation effects

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Skin cancers, though rare in Japan, have reportedly been on the rise, but little else is known about epidemiologic features of different histologic types of skin cancer. The Life Span Study cohort, which consists of 93,700 atomic-bomb survivors, many of whom were exposed to negligibly low radiation doses, and 26,600 people not exposed to radiation, enables a population-based study of spontaneous as well as radiation-related cancer risk. Skin tumor incident cases diagnosed between 1958 and 1987 were ascertained by linkage to the Hiroshima and Nagasaki tumor registries augmented by searches of other data sources. Study pathologists reviewed tumor specimens and pathology reports and classified tumors using the World Health Organization classification scheme. They identified 274 primary incident skin cancers, of which 106 were basal cell carcinoma (BCC), 81 were squamous cell carcinoma (SCC), and 14 were malignant melanomas. Background incidence rates and radiation effects were assessed by Poisson regression models allowing for the effects of demographic and other covariates. BCC and SCC background incidence rates were both about 3 per 100,000 per year. BCCs were mainly on the head/neck (81%), whereas SCCs occurred most frequently on the arms/legs (45%) and head/neck (29%), consistent with the presumed role played by solar UV exposure in skin cancer. The BCC rates increased significantly between 1958 and 1987, whereas the SCC rates remained unchanged. The excess absolute risk of BCC per unit skin surface area related to atomic-bomb radiation exposure did not differ between UV-exposed and shielded parts of the body, suggesting the additivity of the radiation-related and background BCC risks.

Key words: basal cell carcinoma of the skin; squamous cell carcinoma of the skin; ionizing radiation; sun exposure

Skin cancers are relatively rare in Japan. Age-adjusted incidence rates (per 10^5 per year) of melanoma are 0.2–0.5 in Japan compared to that of 10–20 in US whites and 30–40 in Australia.[1] The incidence rates of about 1.0–5.5 for NMSC in Japan are much lower than US white rates of about 250.[1,2] UV radiation is the major cause of skin cancer, involving all 3 major types: BCC, SCC and melanoma in fair-skinned Caucasian populations.[3,4] Except for the reportedly rising incidence of melanoma and BCC of the skin,[5,6] there have been little epidemiologic data on characteristics of skin cancer in Japan, especially by histologic types.

IR has long been known to cause skin cancer, especially BCC,[3,4,7] and we previously reported the IR effect on BCC in the LSS cohort of atomic bomb survivors and controls.[8] A large number of subjects (more than 57,000 or 51%) in this cohort were not or were only negligibly exposed (*i.e.,* at <5 mSv) to radiation from the atomic bombs. This enabled us to analyze the background cancer rates by histologic type, taking advantage of the long-term cancer incidence follow-up.

In our study, we describe the epidemiologic characteristics of background rates for the different histologic types of skin cancer. We also present results from additional analysis of the radiation-related risk, taking into account the size of skin surface area for UV exposed and shielded parts of the body.

Material and methods

Study population

The LSS cohort consists of 93,741 persons who survived the 1945 atomic bombings in Hiroshima and Nagasaki and 26,580 persons who were residents of the city of Hiroshima or Nagasaki but who were not in either city (NIC) at the time of atomic bombings. This cohort has been followed up by RERF since 1950. Cancer incidence is evaluated in a subset of the LSS subjects (n = 112,305) who were alive and not known to have had cancer as of January 1, 1958, when population-based tumor registries were started in Hiroshima and Nagasaki.

To provide descriptive data, we categorized these subjects into ''nonexposed'' and ''exposed'' groups based on the level of exposure to ionizing radiation from the atomic bombs. The nonexposed group of 57,654 consists of *(i)* persons who were atomic-bomb survivors but exposed to <5 mSv (n = 32,342); and *(ii)* persons who were NIC (n = 25,312) (Table I). The former subjects were exposed to almost negligible radiation doses but were within 10 km from the hypocenter ATB, whereas the latter subjects had no exposure because they were temporarily absent from the cities ATB. Although recent analyses of the LSS data for radiation risk assessment have usually excluded the NIC group, which differs in socioeconomic status and background diseases rates,[8,9] our study included them for the following reasons. As reported by Cologne *et al.*,[10] overall mortality rates in the LSS cohort vary with distance (from the hypocenter) in a complicated way, and the NIC rates are actually similar to the background rates for proximal urban survivors (those who were within 3 km from the hypocenter) but differ from those for distal rural survivors (those who were 3–10 km away). The NIC data, therefore, can provide useful information on background disease patterns by time, age and gender.

Abbreviations: AHS, Adult Health Study; ATB, at the time of the bomb; BCC, basal cell carcinoma; ICD-O, International Classification of Diseases for Oncology; IR, ionizing radiation; LSS, Life Span Study; NIC, not-in-city; NMSC, non-melanocytic skin cancer; RERF, Radiation Effects Research Foundation; SCC, squamous cell carcinoma; UV, ultraviolet.

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TABLE I – SELECTED CHARACTERISTICS OF THE STUDY POPULATION

	Nonexposed[1] (n = 57,654)		Exposed (n = 54,651)	
	No.	(%)	No.	(%)
Location in 1945				
NIC[2]	25,312	(43.9)	–	–
Urban[3]	8,777	(15.2)	54,634	(99.9)
Rural[4]	23,565	(40.9)	17	(0.1)
Hiroshima residents in 1945	38,397	(66.6)	38,451	(70.4)
Male	23,870	(41.4)	22,119	(40.5)
Age in 1958, years				
<20	9,806	(17.0)	9,485	(17.4)
20–29	12,470	(21.6)	11,932	(21.8)
30–39	8,877	(15.4)	8,267	(15.1)
40–49	8,392	(14.6)	7,733	(14.1)
50–59	9,049	(15.7)	8,558	(15.7)
≥60	9,060	(15.7)	8,676	(15.9)
Mean	39.6 years		39.5 years	
Mean age in 1987	60.9 years		60.3 years	
Percent deceased in 1987	34.3%		35.4%	

[1]Includes survivors who received radiation doses of <5 mSv and persons temporarily not-in-city (NIC) at the time of the bombings. –[2]Not in city: Hiroshima or Nagasaki residents who were temporarily absent from the cities at the time of the bomb (ATB).–[3]Subjects who were within 3 km from the hypocenter ATB.–[4]Subjects who were beyond 3 km but within 10 km from the hypocenter ATB.

The ''exposed'' group consists of the survivors who were exposed to doses of 5 mSv or more (n = 54,651) and survivors for whom doses could not be assigned due to complex or unknown shielding (n = 6,587) but likely received doses well in excess of 5 mSv because they were within 2 km of the hypocenter.

Case ascertainment

Both melanocytic and nonmelanocytic skin cancers are reportable to the Hiroshima and Nagasaki tumor registries, and these 2 population-based registries were the primary, though not the only, source of information on incident skin cancer cases.[1,11] The Hiroshima and Nagasaki tissue registries, to which benign and malignant tumors have been reported since 1973, were the major sources for histologically confirmed cases. Histologically diagnosed tumor cases are reported to the tissue registries from hospital pathology laboratories, as well as the clinical laboratories that provide diagnostic services to all practicing physicians, clinics and hospitals without pathology labs.[11] In addition, we searched the computer files and records of the RERF pathology program and clinical records, pathology logbooks maintained at major Hiroshima and Nagasaki hospitals and death certificate information for members of the LSS cohort. The follow-up period for this study was from 1958 through 1987. Although a new cancer incidence follow-up is currently underway, it relies on reported cancer diagnoses and does not include a pathology review.

All subjects with a reported diagnosis of any benign or malignant skin tumor designated by the following ICD-O codes[12] were identified: ICD-O topography codes of 173.0–173.9 (skin), 184.1 (labia majora), 184.4 (vulva), 187.4 (penis) and 187.7 (scrotum); plus ICD codes 140 (lip), 154.2 (anal canal), 154.3 (anus, not otherwise specified), 171.0 (cartilage of ear, to which skin tumors may have been misclassified). Two of the study pathologists (MT and ST) reviewed the tumor registry records and other documents and identified 316 tumors as likely skin cancers. All 3 pathologists (MK, MI and TK) then reviewed pathology reports and slides together with available clinical records. When pathology slides were not available or were in poor condition, tissue blocks were obtained and new slides prepared. Each pathologist first reviewed all cases independently and then together to arrive at a consensus diagnosis. All tumors were reclassified using the World Health Organization histologic classification scheme.[13]

Radiation doses

Estimated radiation doses to the skin were obtained from the RERF Dosimetry System 1986 (DS86).[14] This provides individual dose estimates of gamma ray and neutron exposure based on individual exposure history. DS86 shielded kerma dose estimates, computed as the sum of the gamma dose and 10 times the neutron dose, were used as the surrogate weighted skin doses (mSv). Analyses incorporated an adjustment to account for biases in risk estimates that can be expected to arise as a consequence of random errors in the dose estimates for individual survivors. This adjustment was made using the methods developed by Pierce *et al.*[15] with the assumption that the coefficient of variation of the observed dose given the true dose is 35%.

Statistical analyses

Only first primary skin tumors were considered in the analysis because the ascertainment of subsequent primary tumors may be biased in cancer patients and also because of possible effects of treatment for the first tumor. We employed Poisson regression methods to estimate background incidence rates. Data were organized into a detailed table of cases and person-years cross-tabulated over city, gender, location (urban *vs.* rural) and age (13 categories) at the time of the bombings, attained age (18 categories), calendar year (7 categories) and dose (14 categories of dose and a category for unknown dose and 1 for the NIC group) and inclusion in the Adult Health Study (AHS). The AHS is a long-term clinical follow-up program for a subset of the LSS and membership in the AHS could result in a screening effect in cancer detection for this subset. Each cell of this table contained information on the person-years and counts of cases by histologic type (BCC, SCC, Bowen's disease and malignant melanoma) and anatomic location (head and neck, arms and legs, trunk and external genitals) as well as person-year weighted average values of current age, year, age at the time of the bombings and radiation dose. Since cancer ascertainment is limited to the Hiroshima and Nagasaki prefectures, person-years of follow-up were adjusted to reflect immigration and emigration using the method described by Sposto *et al.*[16]

The AMFIT program from the EPICURE risk regression software[17] was used to estimate rates and their confidence intervals. In analyses focusing on description of the background rates, we consider the effects of gender, city, location at the time of exposure, attained-age category (<50, 50–59, 60–69 and ≥70) and calendar-year category (1958–1964, 1965–1972, 1973–1980 and 1981–1987). In estimating radiation risks, we used parametric models to describe the background rates. In these models, the rates varied as a gender-specific power of attained age with additional multiplicative effects for city, year (secular trend) and location ATB.

The excess relative risk (ERR) model (the background rate × (1 + ERR)) and excess absolute risk (EAR) model (the background rate + EAR) were used to describe radiation effects, and they can be written as:

$$\mathrm{ERR}: \lambda(c, g, a, p, s) \times [1 + \rho(d)\ (c, g, a, p, s)], \text{and}$$

$$\mathrm{EAR}: \lambda(c, g, a, p, s) + \rho(d)\ (c, g, a, p, s)].$$

In the model, $\lambda(\bullet)$ describes background skin cancer rates as a function of city (c), gender (g), attained age (a), calendar year (p) and membership in the AHS (s). The functions $\rho(\bullet)$ and $\epsilon(\bullet)$ described the dose-response function and effect modification, respectively. Potential effect modifiers included the covariates c, g, a, p and s. As in earlier analyses of LSS cancer incidence data,[8,9] person-years were adjusted to allow for effects of migration based on data on immigration and emigration in the AHS cohort. This adjustment is necessary because the tumor registries collect information on cancer diagnoses only for people residing in the registry catchment areas at the time of diagnosis.

TABLE II – HISTOLOGIC TYPES OF SKIN TUMORS

	Nonexposed				Exposed			
	1st primaries		2nd primaries		1st primaries		2nd primaries	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Basal cell carcinoma (BCC)	42	(34.4)	1	(14.3)	64	(42.1)	3	(25.0)
Squamous cell carcinoma (SCC)	42	(34.4)	3	(42.9)	39	(25.7)	3	(25.0)
Bowen's disease	18	(14.8)	3	(42.9)	19	(12.5)	4	(33.3)
Malignant melanoma	5	(4.1)	-	-	9	(5.9)	1	(8.3)
Others	15	(12.3)	-	-	21	(13.8)	1	(8.3)
Soft-tissue tumors	1	(0.8)	-	-	6	(3.9)	-	-
Lymphoid-tissue tumors	4	(3.3)	-	-	2	(1.3)	-	-
Other	6	(4.9)	-	-	6	(3.9)	1	(8.3)
Unclassified	4	(3.3)	-	-	7	(4.6)	0	
Total	122	(100)	7	(100)	152	(100)	12	(100)

TABLE III – ANATOMICAL DISTRIBUTION OF BACKGROUND (NON-EXPOSED) BCCS AND SCCS

	Basal cell carcinoma			Squamous cell carcinoma		
	Male	Female	Both (%)	Male	Female	Both (%)
Head and neck	11	23	34 (80.9)	7	5	12 (28.6)
Arms and legs	1	1	2 (4.8)	11	8	19 (45.2)
Trunk	0	4	4 (9.5)	1	2	3 (7.1)
Genital	1	1	2 (4.2)	3	5	8 (19.0)
Total	13	29	42 (100)	22	20	42 (100)

To assess the effects of radiation, we estimated ERR and EAR adjusted for the nominal skin surface area. We assumed that the total skin surface area for the average Japanese was 1.6 m^2,[18] and proportions of the skin surface areas were 9% for the head and neck (2.5% for the face, 6.5% for the scalp and neck), 59% for the arms and legs, 31% for the trunk and 1% for the external genital region.[19] The face and hands were considered to be sun- (or UV-) exposed and the rest of the body to be sun-shielded, with 0.12 m^2 (7.5%) and 1.48 m^2 (92.5%) nominal skin surface area apportioned, respectively. Adjustment for skin surface area was made by multiplication of the nominal surface area (m^2) for the proportion of the body site of interest by the migration-adjusted person years (person-years $\times$ m^2). We provided background and excess incidence rates per nominal surface area (m^2) per 10^5 person-years.

Results

More than 65% of the study subjects were Hiroshima residents and about 60% were women (Table I). The average age of the cohort was 39.5 years at the start of the follow-up in 1958 and 60–61 years at the end of the follow-up in 1987. Ages in 1958 ranged from the early teens to older than 60 years. The distributions of exposed and nonexposed subjects by age, gender and city were generally comparable.

In the cohort of 112,305 subjects, 293 skin tumors were ascertained among 274 persons during the period of 1958–1987. Histologic diagnoses for 282 tumors (96%) were based on actual slide reviews ($n = 261$) or information from pathology reports or hospital records ($n = 21$). Table II presents the breakdown of primary and secondary skin tumors by histologic types. The most common first primary skin tumors were BCCs (106 cases, 39%) and SCCs (81 cases, 30%), followed by Bowen's disease (37 cases, 14%) and malignant melanoma (14 cases, 5%). There were proportionally more BCCs in the exposed (42%) than in the nonexposed groups (34%).

Sixteen subjects developed a total of 19 second primary skin tumors: 8 subjects had 10 other skin tumors diagnosed at the time of the first primary skin tumors (synchronous tumors); another 8 later developed 9 second primary skin tumors during the follow-up period (metachronous tumors). The frequency of second primary skin tumors was 7.3% (12/163) and 5.4% (7/129) in the exposed and nonexposed groups, respectively ($p = 0.50$).

Proportionally more soft tissue tumors occurred in the exposed (6 cases, 3.9%) than in the nonexposed group (1 case, 0.8%), but the difference was not significant ($p = 0.10$) possibly due to the small numbers. Of the 6 soft tissue tumors in the exposed group, 3 were dermatofibrosarcomas (2 female and one male; 2 occurring in the trunk and 1 in the face), and 2 had a skin dose of >100 mSv.

Five cases of SCC developed at the site of a scar caused by heat and burns from the bomb. Four of these cases were about 15 years of age at the time of the bombing. In addition, 9 SCC and 2 Bowen's disease lesions occurred in 7 individuals at the body site previously irradiated for tinea pedis and other skin conditions. Of the 9 SCC cases, 1 was exposed to radiation from the bomb at >100 mSv, 1 at <100 mSv and the remainder had negligible or 0 radiation exposure.

Background incidence

Table III presents tumor locations of BCCs and SCCs in the nonexposed group. The majority of BCCs and SCCs were in those parts of the body usually exposed to UV from the sun, *i.e.,* head/neck or arms/legs. Whereas about 80% of BCCs were in the head/neck region, SCCs were more evenly distributed (45% on the arms/legs, 39% in the head and neck region and 19% in the genital area). Of the 19 SCCs on the arms/legs, 14 were on the leg (8 in males and 6 in females). Bowen's disease lesions largely occurred in the arms/legs (44%) and trunk (39%), and 4 of the 5 malignant melanomas were on the arms and legs (not shown in Table III).

Because the rates varied significantly by attained age and calendar time, adjusted background rates are presented together with crude rates (Table IV). Adjusted rates by attained age were estimated for a person in 1980; adjusted rates by calendar year were for an individual who was 60 years of age at that time; and adjusted rates by city, gender, AHS membership and location at the time of the bombings were estimated for a person whose attained age was 60 years in 1980.

The adjusted BCC rate was slightly higher in Nagasaki (at latitude 32° N), which is further south than Hiroshima (at 34° N), whereas the SCC rate was slightly higher in Hiroshima than in Nagasaki; neither difference was statistically significant, however. The SCC rate was significantly higher in males than in females ($p = 0.03$), but there was no gender difference for BCC rates. The background rates increased significantly with increasing attained age for both BCC and SCC (p for trend <0.001) but slightly more

TABLE IV – BACKGROUND INCIDENCE RATES FOR BASAL CELL CARCINOMA (BCC) AND SQUAMOUS CELL CARCINOMA (SCC) BY SELECTED VARIABLES

Variables	BCC				SCC			
	IR nonexposed group		Adjusted background rate (95% CI)[2,3]	*p*-value[4]	IR nonexposed group		Adjusted background rate (95% CI)[2,3]	*p*-value[4]
	Cases	Crude rate[1]			Cases	Crude rate[1]		
City[3]								
Hiroshima	30	3.57	2.88 (1.55–4.86)		31	3.69	3.46 (2.05–5.45)	
Nagasaki	12	3.10	3.17 (1.48–6.00)	ns	11	2.84	3.22 (1.56–5.94)	ns
Gender[3]								
Male	13	2.74	2.73 (1.28–5.18)		22	4.63	5.06 (2.83–8.36)	
Female	29	3.86	3.09 (1.67–5.19)	ns	20	2.66	2.55 (1.43–4.22)	0.028
Age (attained)[4]								
<50 years	1	0.16	0.25 (0.01–1.13)		2	0.66	0.56 (0.16–1.44)	
50–59	3	1.24	1.55 (0.38–4.06)		7	2.90	2.62 (1.07–5.35)	
60–69	7	3.49	4.52 (1.91–8.92)		6	2.99	2.68 (1.02–5.76)	
≥70	31	17.55	20.2 (13.8–28.3)	<0.001	25	14.15	13.2 (8.23–19.9)	<0.001
Calendar year[5]								
1958–64	3	0.86	1.17 (0.28–8.16)		11	3.15	5.46 (2.81–9.42)	
1965–72	7	2.01	1.86 (0.75–3.86)		9	2.58	3.25 (1.54–5.97)	
1973–80	13	4.30	2.73 (1.32–5.08)		12	3.97	3.71 (1.92–6.44)	
1981–87	19	8.33	3.81 (1.91–6.85)	0.048	10	4.38	3.15 (1.50–5.80)	ns
AHS[3]								
Non-AHS	33	3.23	2.83 (1.53–4.70)		32	3.14	3.12 (1.85–4.89)	
AHS member	9	4.35	3.52 (1.51–7.12)	ns	10	4.83	4.51 (2.12–8.50)	ns
Location ATB								
NIC	16	2.91	2.56 (1.27–4.64)		9	1.64	1.67 (0.75–3.23)	
Urban	7	3.82	3.29 (1.27–7.19)		4	2.18	2.18 (0.65–6.39)	<0.001
Rural	19	3.84	3.34 (1.69–5.95)	ns	29	5.87	5.86 (3.46–9.28)	

AHS, Adult Health Study; ATB, at the time of the bombings; NIC, not in either city at the time of the bomb.–[1]Crude rates among the unexposed group. –[2]Rates per 100,000 person-years by city, gender, AHS membership and location are those at age 60 and in year 1980.–[3]Rates per 100,000 person-years by attained age category are those in year.–[4]Test for homogeneity for city, gender, AHS membership and location; test for trend for attained age and calendar year category are those at age 60.–[5]Rates per 100,000 person-years by calendar year.

steeply for BCC than SCC. We estimated that the BCC rates increased by 11% per year in attained age and SCC rates by 8% per year in attained age.

The BCC rates increased significantly during the period of 1958–1987 (*p* for trend = 0.048). The increase was estimated to be at a rate of 47% per 10-year calendar period at age 60 years. The SCC rates did not change significantly during the same time period. There were too few malignant melanomas for meaningful trend analysis.

To assess variations in background rates, we also grouped nonexposed survivors (with doses <5 mSv) into 2 groups by distance from the hypocenter, *i.e.,* the urban residents who were within 3.0 km from the hypocenter (proximally exposed) and the rural residents who were 3–10 km (distally exposed). The background BCC rates were similar among the urban, rural and NIC groups, but the SCC rate was higher among rural residents than among urban residents or the NIC (*p* for heterogeneity = 0.003). The background rates for malignant melanoma and Bowen's disease did not significantly differ by city or gender (data not shown).

The BCC and SCC rates were slightly and insignificantly higher among AHS subjects than non-AHS subjects. There were too few malignant melanoma or Bowen's disease cases for analyses by demographic or other variables.

Radiation-related BCC risk

We previously reported[8] a significant radiation effect for BCC but not for SCC, and the ERR per Sv was estimated to be 1.8 (90% CI, 0.83–3.3) for BCC and <-0.1 (90% CI, $<-.01$, 0.1) for SCC. The ERR estimate was almost 10 times higher for BCC in parts of the body not heavily exposed to sunlight compared to BCC in the face and hands, but these ERR estimates did not take into account the difference in surface area covering the heavily sun-exposed face and hands and the rest of the body.

Table V presents incidence rates for BCC per 10^5 square meter (of skin surface) person-years. These incidence rates were estimated for a person at age 60 years adjusted for city, gender and AHS membership using the ERR model. The background rate for BCC in the highly sun-exposed part of the body was very high (18.00 per 10^5 m^2 years), and this results from the large number (65%) of BCCs occurring in a small surface area covering the face and hands (7.5% of the total body surface). The smaller number of BCCs in the remaining part of the body translates into a much lower rate of 1.11 (per 10^5 m^2 years).

When tumors in any part of the body were considered, the ERR per Sv for BCC adjusted for gender, city and AHS membership was 1.9 (95% CI, 0.8–3.9) for a person who was 60 years in 1980 (Table V). By tumor location, the ERR for the relatively UV-shielded parts of the body was 3.9, which was several times higher than that of 0.6 for the UV-exposed parts. However, when measured in terms of absolute rates, the excess absolute risk (EARs per m^2 years Sv) of 9.1 for the UV-exposed parts did not significantly differ from that of 5.6 for the UV-shielded parts. This suggests that the much higher ERR for the UV-exposed parts of the body results from dividing the absolute excess risk, which is similar for the UV-exposed and shielded parts, by the much higher background rate for the UV-exposed parts.

Discussion

Because a large number of subjects in the LSS cohort have little or no exposure to atomic bomb radiation, this cohort is an excellent source of population-based cancer incidence data useful for descriptive epidemiology. Histologic diagnoses based on the standardized pathology review in our study add a special strength to the population-based data. Overall skin cancer rates are much lower in Asian populations than in Caucasian populations,[20] and the relative frequencies of histologic types of skin cancer also differ. As expected, the incidence of both melanoma and NMSC was substantially lower in Hiroshima and Nagasaki than in white populations. We also found that, in Hiroshima and Nagasaki, background BCC rates did not exceed the SCC rates, as they do in Caucasian populations. In US whites, for example, the BCC rates are about 5 times higher than SCC rates.[2] However, the anatomic distributions of skin cancers in this population generally resemble the

TABLE V – INCIDENCE RATES EXCESS RELATIVE RISK (ERR) AND EXCESS ABSOLUTE RISK (EAR) PER SURFACE AREA OF THE SKIN FOR BASAL CELL CARCINOMA (BCC)

Site (surface area)	Nonexposed			Exposed			ERR/Sv[2] (95% CI)	EAR/10^5 sq·m years Sv[2] (95% CI)
	Rate / 10^5 sq·m PYs[1]	Cases	Sq·m years (in 10^5)	Rate / 10^5 sq·m PYs[2]	Cases	Sq·m years (in 10^5)		
Entire body (1.600 sq·m)	2.4	26	10.8	3.4	54	16.3	1.9 (0.8–8.9)	5.7 (2.4–10)
UV-exposed sites (face/hands, 0.120 sq·m)	18.0	17	0.8	18.3	20	1.2	0.6 (<0–2.4)	9.1 (< 0–42)
UV-shielded sites (rest of body, 1.480 sq·m)	1.1	9	10.0	2.1	34	15.0	3.9 (1.4–9.3)	5.6 (2.4–10)

[1]Incidence rates at age 60 and in year 1980, adjusted for gender, city and Adult Health Study (AHS) membership (based on ERR model). –[2]ERR or EAR at age 60 and in year 1980, adjusted for sex, city and AHS membership.

patterns seen in Caucasian populations in that both BCCs and SCCs occur predominantly in sun-exposed parts of the body, *i.e.,* the head/neck and arms/legs, with a tendency for SCCs to occur relatively more frequently on the arms/legs than BCCs.[21] Sunlight exposure thus appears to play an important role in the development of skin cancer in the Japanese population. In Hiroshima and Nagasaki, the SCC rates were significantly higher in males than in females but there was no gender difference in the BCC rates. In Caucasian populations, the male:female ratio also tends to be higher for SCC than BCC.[2,21] We found a significant increasing trend of background BCC rates between 1958 and 1987 in Hiroshima and Nagasaki, whereas the SCC rates remained stable during the same period. The increase in BCC rates, but not in SCC rates, has been reported by Ichihashi *et al.*[5] for the period from 1976–80 to 1986–90 based on prevalence data among dermatology patients at university hospitals in Japan.

Our trend data are based on incident cases ascertained largely from the Hiroshima and Nagasaki tumor registries with supplemental case finding using additional data sources. Because of the relative rarity of skin cancers in Japan, NMSCs are routinely reported to the tumor registries in Hiroshima and Nagasaki as well as those in other parts of Japan. The age-adjusted incidence rates of NMSC of 3–5 (per 100,000) in Hiroshima and Nagasaki are higher than that of 1–2 reported from other registries in Japan.[20] The higher Hiroshima and Nagasaki rates are likely due to active case finding through hospital visits and medical record abstraction, compared to the passive case notification system employed by many other registries in Japan. Based on conventional quality-control measures such as the death certificate only (DCO) rate or mortality/incidence ratio (M/I ratio), the Hiroshima and Nagasaki incidence data are considered among the best in Japan.[11] Although DCO rates and M/I ratios are not relevant for mostly nonfatal skin cancers, we believe that the high case ascertainment rate demonstrated by these measures would also apply for skin cancers because the completeness of case ascertainment largely depends on how extensively the numerous sources of cases are used for case finding. This is indirectly supported by the finding that 80% of skin cancer cases were ascertained from 2 or more sources and 33% from 3 or more sources and that these proportions are comparable to those for other solid cancers.[11]

In the US, relatively benign cancers are increasingly treated as outpatients, and the failure to access cases from these sources would result in underestimating skin cancer incidence.[22,23] In Hiroshima and Nagasaki, this is an unlikely problem because we reviewed the records of pathology laboratories that provide services to practicing physicians and outpatient clinics. Furthermore, incomplete ascertainment from these sources would have underestimated, rather than contributed to, the trend for increasing BCC incidence over time that we observed in our study. The stable trend in rates for SCC, which is more fatal than BCC, also provides some evidence that the case ascertainment was quite good. The increase in BCC rates, but not in SCC rates, reported by Ichihashi *et al.*[5] based on data from sources completely different from ours adds credibility to the present trend data.

Among the additional case-ascertainment efforts used for our present study, most systematic and important were the tissue registries in that these enabled the histologic review of both benign and malignant tumors collected in the area starting in 1973. The impact of the tissue registry on the BCC trends was not evident, however, as the increasing trend was seen before and after 1973 (Table IV). The RERF surgical and autopsy pathology program, which was active during the 1950 and ’60s may have contributed to the identification of histologically diagnosed cases during the pre-tissue registry era. We were unable to review some tumorlike lesions, such as actinic keratosis, senile keratosis and leukoplakia, which are not routinely reported to the tissue registries. Some of these lesions may be precursors of SCC or misclassified SCCs in earlier years. This would have led to underestimation of SCC rates, but not BCC rates, in the earlier years of follow-up.

BCCs are slow growing and mostly localized tumors, and improved tumor detection and diagnosis by increased awareness by physicians and/or patients should also be considered. Although being a member of the AHS clinical subcohort study increased the baseline skin cancer rates only slightly and insignificantly (Table IV), this does not reject the possibility that the detection and diagnosis of benign skin lesions has generally improved over the decades. The extent to which such a change would have affected the BCC trend is difficult to estimate because of the lack of any systematically kept clinical records over the 30-year period. For example, if a benign skin lesion had been overlooked by a physician and no tissue specimen obtained, it would have been extremely difficult to identify from the existing documents.

Although we had too few malignant melanoma cases for meaningful trend analysis, a significant increase in melanoma rates has been found in women in Osaka.[6] The recent increase in BCC and melanoma rates may be another unique feature of skin cancers in Japan. In Caucasian populations, increasing trends of skin cancer have generally involved all 3 types: BCC, SCC and malignant melanoma.[21] The lack of increasing SCC rates in Japan is in especially sharp contrast to the rapid increase in SCC rates (230–350%) compared to that of BCC rates (80%) in New Hampshire.[24]

It has been suggested, based on a meta-analysis of epidemiologic data, that SCC is most strongly associated with total lifetime sun exposure, especially with occupational exposure, whereas both BCC and melanoma are more strongly associated with non-occupational (intermittent) sun exposure and history of sunburn.[3,25] It may be that total and occupational sun exposures are the predominant cause of skin cancer in Japan, contributing to the relatively high SCC rate, especially in males. The higher incidence of SCC in rural residents than urban residents or NIC in our study may reflect the differences in occupational background. The NIC, who were absent at the time of the bombs, were socioeconomically similar to the urban residents. The increasing trend in melanoma incidence observed in Osaka was derived from the increase in tumors of the extremities in women, and it was thought to be due to recent changes in clothing styles in Japanese women.[6] Because of the small numbers of BCC cases in our study, further analyses by age, gender and tumor location were not possible. However, since the majority of BCCs were in the head and neck, more frequent outdoor activities, and possibly a decrease in hat and parasol use, are consistent with the general increase. An analysis of skin cancer trends based on the much larger number of cases diagnosed in the total populations of Hiroshima and Nagasaki is planned, and it should provide further insights into the time-related incidence patterns.

The apparently high proportion of SCCs in the genital areas (19%, Table III), compared to less than 3% in US whites is noteworthy,[2] but the present finding is based on few cases. Our data indicate the need for further study in a larger population, with a focus on genital skin cancer in relation to human papilloma virus.[26]

Despite the recent increase, the current BCC rates still have not surpassed the SCC rates in Japan. The unusual similarity in BCC and SCC incidence rates in Japanese has also been suggested by a study of NMSC[27] in the Japanese residents of Kauai, Hawaii, where the BCC rates are extremely high in other population groups.[28] The BCC rates of 29.7 per 10^5 in Japanese Kauai residents, though much higher than those in Japan, were only slightly higher than the SCC rates of 22.9.[27] The pigmented skin in Japanese may be more resistant than fair Caucasian skin against intense and intermittent sun exposures. There is, however, considerable variability in skin color and sun sensitivity among Japanese.[5,29] An increased risk of actinic keratosis has been found among persons who tend to develop sunburn, and especially among those who experienced severe sunburns with blister formation during childhood.[30] More studies are needed to clarify the role of various types of UV exposure and host factors for different types of skin cancer in the Japanese population.

Although animal data suggest a synergistic interaction between repeated UV and ionizing radiation for skin tumors (ICRP Pub 59, Fry 1990), little is known about the nature of joint effects of the 2 carcinogens in human. In a study of patients irradiated for tinea capitis in New York, Shore *et al.* reported that the excess risk for BCC per unit dose per unit skin area was significantly higher for the UV-exposed margin of the scalp (21/100 cm^2 per Gy) than for the relatively UV-shielded scalp (4.7/100 cm^2 per Gy).[31] In our study, the EAR estimate per unit skin area for the UV-exposed face and hands was only insignificantly higher than for the UV-shielded parts of the body. Our findings are consistent with the uniform distribution of the IR-related excess risk over the body, suggesting that the IR-related risks are additive to the background rates, although the limited statistical power should be recognized. In estimating the risk per skin surface area, we assumed that 7.5% of the total body surface of 1.6 m^2 was UV exposed. Although the total body surface area may vary with body height and weight, gender and other factors,[32] the proportion of surface areas for anatomic sites, especially of the UV-exposed face and hands, appears less influenced by gender, ranging narrowly between 7% and 8% by age and gender in Japanese.[33] The extent of UV exposure, especially at the target cell level, is also not characterized. These may in part explain the different results regarding the modifying effect of UV exposure on the IR-related risk between the New York tinea capitis and our populations.

Our study provided population-based descriptive data on skin cancer in a Japanese population. The anatomic distribution of skin tumors is consistent with the notion that UV exposure from the sun is the major determinant for NMSCs and possibly malignant melanoma. The relative frequency of BCCs and SCCs, gender differences and the temporal trend, however, suggest several unique aspects of the sunlight exposure-skin cancer relationship in this population, which may be influenced by pigmentation and behavioral factors. Our finding of a rapid rise in BCC incidence suggests that an educational campaign about the dangers of UV exposure might be warranted.

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